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MULTIPLE EFFECTS OF SOMATOSTATIN ANALOGS VERIFIED IN THREE CASES OF METASTASIZED NEUROENDOCRINE TUMORS OF THE GASTROENTEROPANCREATIC SYSTEM

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Aims and background: In neuroendocrine tumors of the gastroenteropancreatic (GEP) system, radiolabeled analogs of somatostatin (SST) are useful to the surgeon in different phases of treatment: preoperatively, to identify the lesion with somatostatin receptor scintigraphy (SRS), intraoperatively for localization using a hand-held gamma probe, and postoperatively acting directly to eliminate any residual tumor cells. Additional features of these analogs that are of value in treating such GEP tumors include their antiproliferative potential, which is in the process of being verified, and, above all, their anti-secretory action, so effective in symptom control. In this study the authors, based on their own experience, evaluate the effectiveness of SST analogs in treating GEP endocrine tumors.

Methods: Three patients with malignant GEP apudomas were studied. In case 1, an insulinoma, the patient underwent four surgical procedures for ablation of the pancreatic tumor and of hepatic and lymph node metastases in addition to local radiofrequency treatment and radiometabolic therapy. Case 2 was a carcinoid tumor of the small intestine with hepatic metastases, managed by ileal resection, local radiofrequency treatment and receptor-mediated radionuclide therapy. In case 3, a non-functioning pancreatic carcinoma with liver and lymph node metastases, the patient underwent four surgical procedures, hepatic chemoembolization, antiproliferative treatment using octreotide (OCT) and metabolic radionuclide therapy.

Results: In all three cases SRS proved highly sensitive in the early detection of even the smallest recurrences. There was uncertainty, however, regarding the effectiveness of therapy with radiolabeled SST analogs. Hepatic metastases from the carcinoid were completely unresponsive, but in the case of the insulinoma, the hepatic metastases showed necrosis following treatment, while lymph node metastases were unaffected. In the case of the non-functioning carcinoma, there was a correlation between treatment and a marked improvement in the patient's clinical condition, although the appearance of the lesions themselves remained unchanged. The antiproliferative effect of OCT in this case was nil.

Conclusions: SRS proved highly accurate in detecting recurrences during follow-up. The merits of radiometabolic therapy, on the other hand, were unclear, a finding reported elsewhere in the literature, and in the only case treated by prolonged OCT treatment, no antiproliferative action was observed. The diagnostic usefulness of SRS was thus confirmed and it appears likely that radiolabeled analogs used intraoperatively for tumor localization will prove equally of value. The effectiveness of receptor-mediated radionuclide therapy is still in the process of being verified. Based on the expectation of analogs with an universal affinity for SST receptors (sst), it is reasonable to look forward to a significant increase in the efficacy of this type of therapy.

Key words: apudomas, GEP neuroendocrine tumors, octreotide, radiometabolic therapy, somatostatin receptor scintigraphy.

Introduction

It is not unusual for certain insulinomas and gastrinomas to escape preoperative detection as well as intraoperative identification because of their small size and/or particular localization. According to Cirillo *et al.*¹ and Ressetta *et al.*², this occurs in 10-30% of cases, while Adams and Baum³ reported such a situation in 20% of insulinomas and 40% of gastrinomas. This circumstance may even persist in the presence of evident metastases, particularly in cases of gastrinoma. From the surgeon's point of view, this is the most baffling aspect of neuroendocrine tumors, although nuclear medicine technologies are now capable of providing valuable, often critically important assistance. It is in this context that the synthetic analogs of somatostatin (SST) labeled with radioactive isotopes come into play, since they make it possible to preoperatively image occult lesions with scintigraphy and to localize them intraopera-

tively using a hand-held gamma probe. With respect to scintigraphy, the intraoperative probe has the advantage of depicting the lesion with great precision in terms of both size and topographic location, although the slow clearance of the tracer from surrounding tissues in addition to its accumulation in the liver, the kidney and the spleen must be taken into account.

Patients and methods

Our study involved 3 patients with different types of malignant gastroenteropancreatic (GEP) apudoma.

Case 1

The first patient was a 64-year-old woman who, at the age of 39, had undergone enucleation resection of an insulinoma of the pancreatic body, the histological nature of which was uncertain. Seventeen years later,

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the patient presented with a frankly carcinomatous recurrence associated with sporadic episodes of hypoglycemia. Left pancreatectomy and splenectomy were performed, resulting in definitive remission of the hypoglycemic syndrome. After an interval of 22 years from the original procedure, 2 large paraaortic metastases at the level of the renal vessels (Figure 1) and two hepatic metastases located in segment VI of the liver were treated in a single surgical session by resection and radiofrequency therapy, respectively. Three months later, a follow-up CT exam showed the presence, confirmed by somatostatin receptor scintigraphy (SRS) with ^{111}In -pentetreotide, of another enlarged paraaortic lymph node. In the years that followed the first reoperation, the patient's plasma concentrations of chromogranin A (CgA) (173.1-274.2 ng/mL, normal value <123 ng/mL) and pancreatic polypeptide (PP) (77.7-268 pg/mL, normal value <85.8 pg/mL) rose by varying increments. The scintigraphic exam carried out during the first cycle of radiometabolic therapy with ^{90}Y -DOTA0-Tyr3-octreotide (^{90}Y -DOTATOC) showed, in

addition to the paraaortic uptake, a suspicious area of concentration in segment VI of the liver, which was subsequently confirmed by US and MRI. After 4 cycles of therapy (total MBq: 4,932) with intervals of 6 weeks between treatments, the size of the lesions appeared unchanged at CT and the levels of plasma CgA and PP remained elevated (425 ng/mL and 476 pg/mL, respectively), while SRS was inconclusive. A fourth surgical procedure was then performed, this time consisting of a wedge resection of segment VI of the liver to remove the mass confirmed at intraoperative US and the resection of two lymph nodes in the vicinity of those previously removed.

The surgical specimen was fixed in buffered formalin and the entire hepatic lesion was sampled for histological evaluation. In addition, immunohistochemical staining for endocrine markers was performed. On histological examination the lesion was mainly constituted by an eosinophilic non-homogeneous necrotic area surrounded by a collagen rim (Figure 2). Rare clusters of endocrine neoplastic cells were found in the context of the necrotic hepatic area. Moreover, neoplastic cells were found in two resected lymph nodes. No neoplastic cells were observed in the hepatic resection margins. The endocrine phenotype of the residual neoplastic cells was confirmed by immunohistochemistry (insulin, synaptophysin).

During the postoperative course, the patient's plasma CgA was found to be unusually elevated (>700 ng/mL), a finding related to treatment with omeprazole. When use of the drug was discontinued, the CgA level returned to normal (82.1 ng/mL).

Case 2

The second patient was a 62-year-old male who, at the age of 48, had undergone a left hemicolectomy for

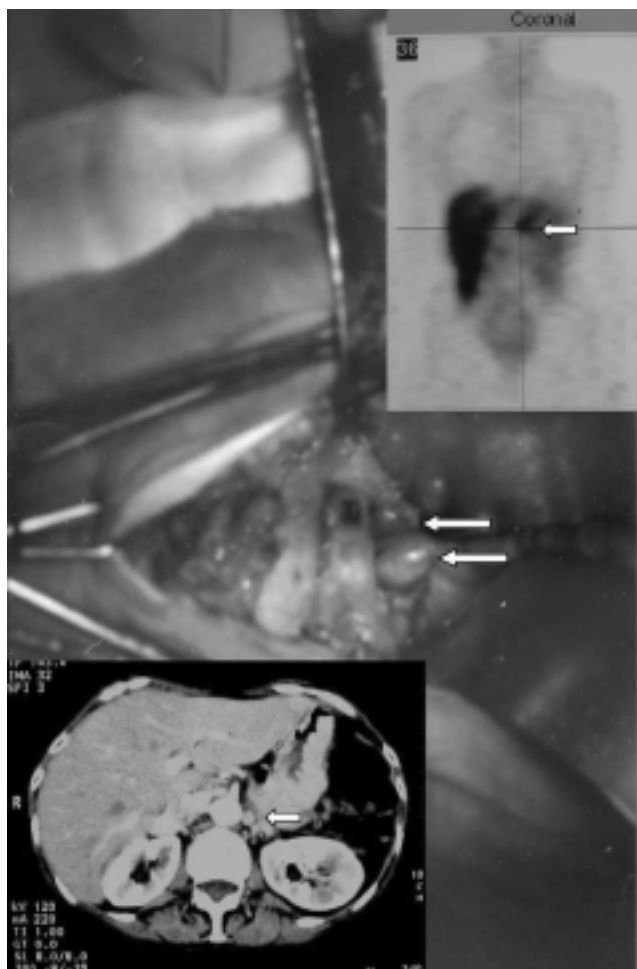


Figure 1 - Two paraaortic lymph node metastases (arrows) on CT/scintigraphic scans and at surgery.

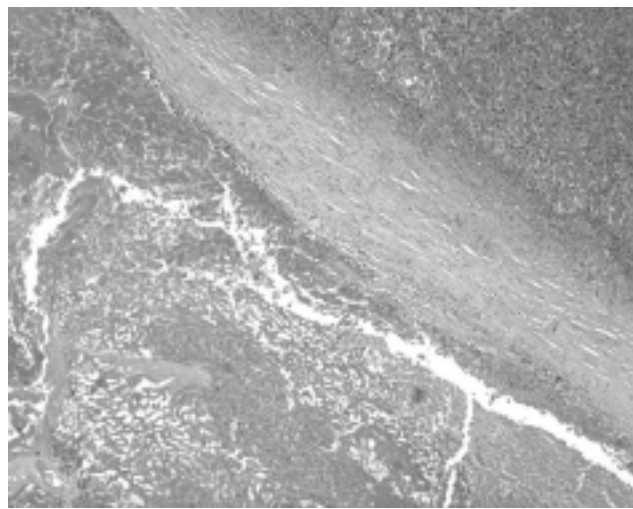


Figure 2 - Large necrotic area surrounded by a collagenous rim. The hepatic tissue outside the lesion is normal.

carcinoma of the colon. Ten years later, during follow-up, the patient, who was asymptomatic, was found at US, CT and MRI to have multiple hepatic lesions which were thought to be of an angiomatous nature. Three years later, because of the increase in the number and size of these lesions, a new MRI using the superparamagnetic contrast agent Endorem® was carried out, the result of which was suggestive of metastasis. This was confirmed by cytological analysis of the needle-aspiration biopsy, which resulted in a diagnosis of "neuroendocrine neoplasia". The definitive diagnosis of ileal carcinoid tumor with metastasis to the liver was based on elevated plasma levels of serotonin (5-HT) (538 ng/mL, normal 90-180 ng/mL) and PP (121.7 pg/mL, normal <85.8 pg/mL) and an increase in urinary 5-hydroxyindole acetic acid (5-HIAA) (17.5 mg/24h, normal 2-6 mg/24h). SRS showed multiple areas of uptake in the liver and in the right mesogastric zone. Surgical treatment consisted of resection of a 105 cm length of ileum in which there were 7 small tumor foci located 10-15 cm apart (Figure 3). A superficial liver metastasis was also excised, while 6 additional liver lesions were treated by US-guided radiofrequency ablation. Treatment of an ulterior liver lesion adjacent to the vena cava was deemed unfeasible. Sixteen of the 17 lymph nodes removed at the origin of the upper mesenteric artery showed tumor infiltration. Four cycles of radiometabolic therapy using ^{90}Y -DOTATOC at 6-week intervals for a total of 5,720 MBq produced no appreciable effect on the residual metastasis, as confirmed by CT and scintigraphy. While the levels of plasma 5-HT (270 ng/mL) and urinary 5-HIAA (12.1 mg/24h) remain elevated, the patient is currently in satisfactory condition, with no symptoms.

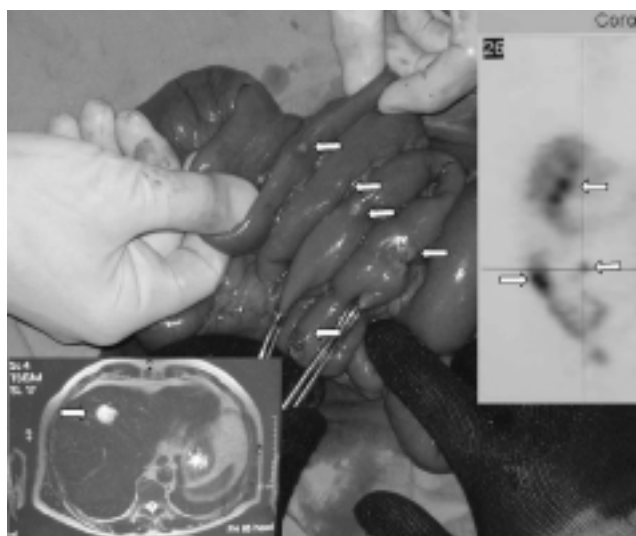


Figure 3 - Multiple ileal localizations of a carcinoid tumor with metastasis to the liver; at the lower left, MR image of a liver metastasis (arrow); at the upper right, scintigraphic scan showing areas of uptake in the liver and the right mesogastric zone.

Case 3

The third patient was a 57-year-old man who, at the age of 47, had undergone a cephalic duodenopancreatectomy for a non-functioning neuroendocrine tumor of the head of the pancreas and excision of three metastatic lesions located in liver segments V, VI and VII. Recurrence of the disease after four years required a wedge resection for a metastasis in segment VIII of the liver. Three courses of hepatic chemoembolization were carried out at brief intervals, the latest 4 years ago, using streptozotocin and lipiodol plus gelatin sponge (Spongel) as the embolizing agent. Subsequently, octreotide (OCT) therapy was administered in two different formulations, first with immediate release (IR) (0.5 mg daily for two years) and then with long-acting release (LAR) (30 mg every four weeks for 18 months until metabolic radionuclide therapy was initiated). The effects of both OCT therapy and chemoembolization, however, proved negligible. In October 2003, 9 years after the first surgical procedure, the patient was operated on again, this time for excision of a large collection of lymph nodes at the origin of the upper mesenteric artery. In January 2004, US and CT monitoring showed hepatic recurrence (three lesions <1 cm) confirmed by SRS, as well as new lymph node metastases at the site mentioned above (Figure 4). Radionuclide therapy (4 cycles of ^{90}Y -DOTATOC administered at six-week intervals for a total of 6,138 MBq) coincided with clinical improvement, specifically a weight gain of 10 kg and the disappearance of epigastric and lumbar pain which, until then, had been experienced by the patient almost daily. No such improvement,

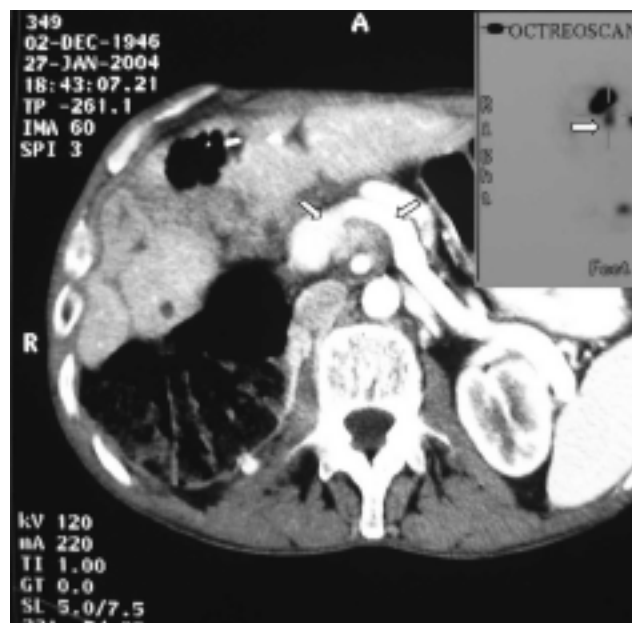


Figure 4 - CT image of a large collection of lymph nodes at the origin of the superior mesenteric artery and the corresponding area of intense uptake at octreotide scintigraphy; CT also clearly depicts multiple hypodense foci in the liver as well as hypertrophy of residual liver segments resulting from prior metastasectomy.

however, was observed on CT and scintigraphic images, nor was there any decrease in plasma CgA (320 ng/mL, normal ≤ 123 ng/mL).

Results

The wide range of diagnostic and therapeutic possibilities anticipated for the synthetic analogs of somatostatin with regard to GEP endocrine tumors was only partially verified in the present study. Among the feasible goals of these analogs in clinical practice, only those concerning preoperative diagnosis and postoperative therapy (particularly antiproliferative and metabolic radionuclide therapy) were tested. The fact that none of the three patients studied had clinical manifestations linked to an endocrine function of the tumor in question rendered any assessment of the effect on symptoms meaningless. In previous clinical observations we had seen that OCT is rarely effective against a hypoglycemic syndrome caused by insulinoma (only 2 remissions out of 13 cases treated). In the only case of glucagonoma studied, the action of OCT was rapid and total, whereas the biochemical effect was extremely limited^{4,5}.

In all three cases described in this study, the diagnostic sensitivity of SST analogs using a radioactive marker for the early detection of even very small tumor recurrences in the course of long-term follow-up was confirmed. Use of SRS, in fact, repeated periodically in each case, demonstrated high overall accuracy. The negative result obtained in the case of liver metastases from an insulinoma is very likely attributable to the necrosis of much of the metastatic tissue, as evidenced by histological examination (Figure 2). We had no occasion to verify the effectiveness of this modality in what would be the logical sequence to its use for diagnosis, i.e., for the intraoperative radioguided localization of tumor lesions.

As far as receptor-mediated radionuclide therapy is concerned, there is much uncertainty regarding its effectiveness. Liver metastases from the carcinoid tumor showed no response to treatment, while the liver metastasis from the insulinoma underwent near total necrosis, although lymph node metastases in the same case were unaffected. In the case of the non-functioning carcinoma, the patient's clinical condition showed marked improvement after just two treatment cycles, a circumstance, however, clearly inconsistent with the information provided by imaging studies. At any rate, we feel that it is worthwhile to persevere in researching this modality. It would be an error to ignore the potential of a vehicle capable of delivering a quantity of radioactivity to the interior of tumor cells a hundred times that transmitted to normal tissue.

An attempt to use OCT for its antiproliferative action was made only in the case involving the non-functioning metastasized tumor. Treatment was continued for a period of three and a half years with no observable effect.

Discussion and conclusions

Clinically, ample use has been made of the well-known inhibitory action of SST and its synthetic analogs on endocrine and exocrine hyperfunction associated with inflammation, hyperplasia and neuroendocrine tumors of the gastrointestinal tract. This effect is based on the interaction with SST receptors (sst)1-5 in the membrane of target cells. Natural SST has an affinity for all 5 receptor subtypes, while OCT, the analog most commonly used, has a strong affinity for sst2 and a much lower affinity for sst subtypes 3 and 5. Insulinomas, unlike other GEP endocrine tumors, are poorly endowed with these receptors, and consequently symptoms in this type of lesion are typically unaffected by OCT treatment. They may even worsen due to the analog's concomitant inhibitory effect on the release of glucagon and GH.

The interaction of SST or its analogs with specific receptors is utilized not only to control symptoms but also diagnostically (SRS) and therapeutically (radiometabolic therapy): octapeptide analogs radiolabeled with ¹¹¹Indium, ⁹⁰Yttrium and ¹⁷⁷Lutetium reach the surface of the tumor cells where they are taken up and internalized by means of endocytosis in the lysosomes of the cytoplasm and subsequently in the DNA of the nucleus. Thanks to this feature, such tumors become sources of radioactivity which can be externally detected with the proper imaging technique. At the same time, the energy produced by the electromagnetic radiation gives rise to ionization phenomena in the tumor tissue itself. If the half-life of the radioisotope is of adequate duration, as in the case of ¹¹¹In-pentetreotide, a single dose should suffice to carry out preoperative scintigraphy, radioguided intraoperative localization, and postoperative scintigraphy. Of course, this capability depends on an appropriate protocol, with imaging carried out no earlier than 24-48 hours from the administration of the marker, so that it can be cleared from the circulation, from the parenchymous organs and from the intestine.

Our experience enabled us to confirm the diagnostic usefulness of octreotide. Therapeutically, however, it proved to be of scant and fluctuating effectiveness, characteristics which would appear to be linked to the limited affinity of OCT for SST receptors. Newly available analogs capable of interacting with all or most of these receptor subtypes give promise of a heightened therapeutic potential, much like that of radioiodine in differentiated thyroid carcinomas. This prospective is already an experimental reality with regard to the analog SOM230, the universal ligand of all sst subtypes except sst4^{6,7}.

For the moment, however, the therapeutic efficacy of OCT remains basically unreliable. Paganelli *et al.*⁸, Cucurullo *et al.*⁹, and Lombardi and Pivonello¹⁰ all report the remission of symptoms in approximately 15% of cases, a reduction in the tumor mass in 25%, stabilization in 35-55%, a >50% decrease in incretion in 81%, and a total lack of response in 20%. Ricci *et al.*¹¹, on the other hand,

reports a single objectively positive response (naturally partial) out of 15 patients treated and a biochemical/symptomatic response in roughly half of the patients.

The outcome of therapy in the three cases reported is equivocal: ineffectual in treating hepatic metastases from the carcinoid, positive for hepatic metastases from the insulinoma, and apparently of considerable benefit in terms of the patient's general condition in the metastasized non-functioning carcinoma of the pancreas, despite the absence of any evident modification of the lesions at scintigraphy and CT.

In addition to inhibiting the production and release of substances that interact as hormones, SST and its analogs seem to have a direct antiproliferative effect on tumors, limiting their increase in volume and, in some cases, even reducing it^{12,13}. To obtain such results, it is

necessary to maintain high plasma levels of the drugs, a condition made possible by the use of slow-release preparations to be administered once every two to four weeks. In our case (no. 3), however, this effect was not observed.

Overall, our limited experience confirms that an interdisciplinary approach in the treatment of GEP endocrine tumors, involving the use of debulking surgery, radiofrequency therapy, chemotherapy, chemoembolization, radiometabolic therapy, interferon and SST analogs, results in a more favorable outcome. We also came to the conclusion that in this particular category of tumors, even when dealing with malignant, metastasized and diffuse lesions¹³⁻¹⁵, one must not yield to an attitude of resignation. Reasonably aggressive treatment often produces results thought to be unobtainable.

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